



**Joslin
Diabetes
Center**

Dedicated to the
study of diabetes
and the care of
those with diabetes

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Dockets Management Branch
US Food and Drug Administration
Department of Health and Human Resources
Room 1061, HFA-305
5630 Fishers Lane
Rockville, MD 20852

Docket Number 98P-0622

To Whom it May Concern:

I would like to express my strong opposition to the petition filed by Public Citizen Health Research Group regarding Rezulin® (troglitazone) tablets and urge that the petition be denied for the reasons outlined below.

First, Rezulin is a unique and highly effective oral medication for the treatment of type 2 diabetes mellitus that has already benefited over one million patients with this common and devastating disease. It is the first drug of its class, the thiazolidinediones, to be made available for clinical use and its unique mechanism of action to reduce insulin resistance gets at the core defect in the vast majority of people with type 2 diabetes. In carefully conducted clinical trials it has been shown to be effective in improving glycemic control and reducing insulin resistance in patients with type 2 diabetes when used either alone as monotherapy (Maggs et al, Ann Intern Med 1998; 128:176-185) or when used in combination with sulfonylureas (Horton et al, Diabetes Care 1998; 21:1462-1469), Metformin (Inzucchi et al N Engl J Med 1998; 338:867-872), or insulin (Schwartz et al, N Engl. J Med 1998; 338:861-866).

Second, we have learned from the United Kingdom Prospective Diabetes Study (UKPDS) that type 2 diabetes is a progressive disease that requires an aggressive stepped-care approach using a combination of lifestyle modification and multiple pharmacological interventions to achieve and maintain currently accepted levels of glycemic control with the goal of preventing or reducing long term complications (UKPDS Group, Lancet 1998; 352:837-853). No single medication used in this landmark study was able to provide sustained glycemic control, resulting in the need for combination therapy in the majority of patients. This is also the common experience of clinicians in the United States and has led to the use of two or more different classes of oral medications having

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different mechanisms of action or the combination of oral agents plus insulin to achieve and maintain glycemic targets in patients with type 2 diabetes. Rezulin has proven to be an extremely valuable agent in this regard because of its efficacy and unique mechanism of action.

Third, Rezulin is very well tolerated by the vast majority of patients who are taking it. Except for the rare cases of hepatotoxicity, there are very few side effects. Since its release in March 1997, we have prescribed Rezulin for over 2000 patients at the Joslin Clinic in Boston, MA. An occasional patient has experienced some fluid retention which has usually responded promptly to diuretics, some patients have gained 5 to 10 pounds in weight associated with improved glycemic control and only a very few have experienced asymptomatic increases in hepatic transaminases that have returned to normal when the medication was discontinued. We have not had any patient develop severe hepatotoxicity leading to jaundice or liver failure, consistent with the much larger data base gathered nationally that demonstrates that the current guidelines for monitoring liver function in patients treated with Rezulin do, in fact, work well.

Based on the above, I believe it is clear that the benefit to risk ratio is very favorable for Rezulin and that with proper monitoring of liver function tests the rare cases of severe hepatotoxicity have been and will continue to be reduced to an acceptable level. The available data already demonstrate that the monitoring program currently in place is effective and has resulted in a marked reduction of severe adverse events in patients treated with Rezulin. Therefore, Rezulin should **not** be banned for use in the treatment of type 2 diabetes mellitus as petitioned by Public Citizen Health Research Group but should continue to be made available to the many millions of people with type 2 diabetes who will benefit from it.

Sincerely yours,



Edward S. Horton, MD
Vice President & Director of Clinical Research
Joslin Diabetes Center
Professor of Medicine
Harvard Medical School

CC: Kathleen Reedy, RDH, MS
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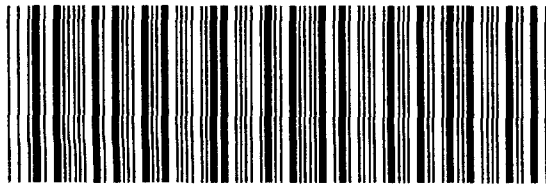
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